PATENT
Attorney Docket No.: 021706-000810US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 1659
Tony Wai-Chiu So *et al.*	Examiner: Sharmila S. Gollamudi
Application No.: 10/124,197	Technology Center/Art Unit: 1616
Filed: April 16, 2002	DECLARATION
For: PHARMACEUTICAL COMPOSITION	

I, Albert Zorko Abram, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I am currently employed by Connetics Australia Pty Ltd, the assignee of the subject application.

3. I am a Senior Chemist-Technical IP Associate and have been in pharmaceutical research since 1987. I have been employed doing dermatological product development for the last 16 years. My *Curriculum Vitae* is of record.

4. I have read and I am familiar with the contents of the above-referenced patent application. In addition, I have read the Office Action dated October 17, 2003 and the Advisory Action dated February 17, 2004 received from the Patent Office in connection with the above-referenced application. It is my understanding that the Examiner alleges that the claimed invention is obvious in view of the disclosures of Navarro (WO 97/03638) in view of Weiner (WO 97/12602), in further view of Leitch (U.S. Patent No. 5,753,216). More particularly, it is my understanding that the Examiner alleges that Navarro discloses a minoxidil composition comprising:

a) 0.1 to 3% by weight of minoxidil;
b) 0.1-3% by weight of a γ-cyclodextrin;
c) 0.5-15% by weight of a solvent; and
d) 30-50% by weight of a monoalcohol.

However, the Examiner admits that Navarro does not teach or suggest the addition of an acid, as is instantly claimed, but this deficiency is supplemented by the disclosure of Weiner (WO 97/03638). Weiner allegedly describes modifying the solubility of a therapeutic material by adding an acid. The Examiner alleges that since Weiner describes the addition of an acid to a minoxidil solution, it would have been obvious to combine the teaching of Navarro with Weiner, in view of Leitch to arrive at the presently claimed invention. Leitch was cited by the Examiner as showing that aerosols are known in the hair care art.

5. The fundamental basis of the Navarro composition is the inclusion of a γ-cyclodextrin compound, which acts to improve the solubility of minoxidil and the cosmetic touch properties of the hair and skin areas to which the minoxidil solution is applied.

6. The present invention relates to a homogeneous aerosol composition comprising:

> a) 5% or greater of a piperidinopyrimidine derivative (e.g., minoxidil)
>
> b) **an acid** selected from the group consisting of hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, citric acid, acetic acid, succinic acid, maleic acid, benzoic acid, lactic acid and mixtures thereof;
>
> c) a solvent of water and a lower alcohol in a ratio of 1:9 to 9:1 by volume;
>
> d) a co-solvent of a polyhydric alcohol selected from 1,3-butylene glycol, polyethylene glycol, hexylene glycol, dipropylene glycol, glycerol or propylene glycol at less than approximately 10% by weight;
>
> wherein the final product of the homogeneous aerosol formulation is a foam or mousse.

The addition of **an acid** to the instantly claimed composition is a critical feature of the present invention as it is the acid component that improves the solubility of the piperidinopyrimidine derivative (e.g., minoxidil) in solution and thus provides compositions that are advantageous, in part, because they can contain higher concentrations of the active ingredient (e.g., minoxidil) than are found in the compositions described in the prior art.

7. The Examiner further alleges, in regard to the obviousness rejection over Navarro in view of Weiner and Leitch that since the instant claims contain open language, the claims do not exclude additional components, such as lipid vesicles, to the composition (see, Advisory Action dated February, 17, 2004, page 3, lines 3-5). Following this logic, it is my understanding that the Examiner alleges that the present claims, by reciting "comprising," does

not exclude the possibility of having a cyclodextrin compound, and as such, the present claims are rendered obvious by Navarro in view of Weiner and further in view of Leitch. I respectfully disagree with the Examiner on this point.

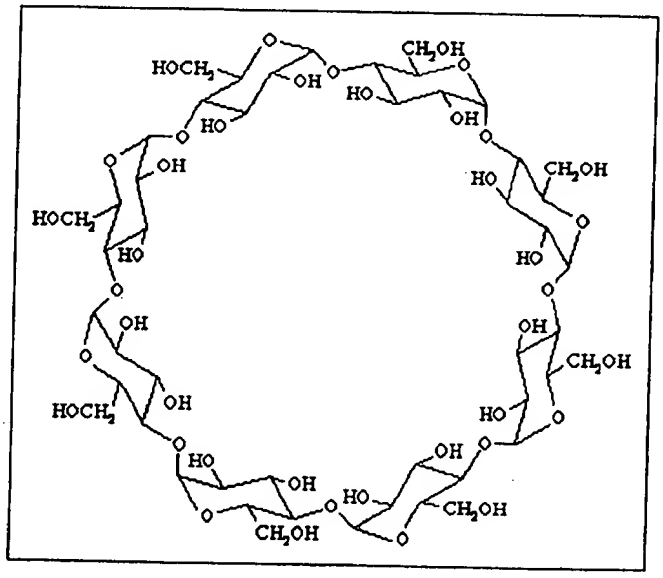
8. According to MPEP § 2143.01, in making a *prima facie* case of obviousness, the Examiner's proposed modification **cannot** render the prior art unsatisfactory for its intended purpose.

> MPEP § 2143.01:
> If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, **then there is no suggestion or motivation to make the proposed modification.**[Emphasis Added] *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

9. It is my scientific opinion that supplementing the teaching of Navarro with the teaching of Weiner **would destroy** the intended purpose of the Navarro composition. Navarro discloses the addition of γ-cyclodextrin to a minoxidil composition to improve the solubility of minoxidil in solution and also to improve the cosmetic touch properties of the solution when applied to hair and skin.

10. Cyclodextrins are polysaccharide molecules consisting of D-glucose units that are linked through glycosidic bonds to form a ring. In particular, γ-cyclodextrin is made up of eight glucose units.

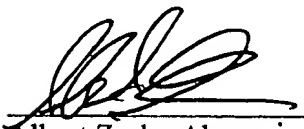
γ-Cyclodextrin



The role of cyclodextrin in Navarro is to function as a host molecule to trap the minoxidil "guest" molecule inside the ring. It is this minoxidil-cyclodextrin "host-guest" complex that imparts improved solubility properties, as compared to a similar minoxidil composition not having cyclodextrin. (see, highlighted sections of Appendix 1, Morrison & Boyd, *Organic Chemistry*, 5th ed., 1987). The glycosidic bonds in cyclodextrin are **acid labile** and it is a scientific fact that subjecting cyclodextrins to acidic conditions will result in the degradation of the cyclodextrins into its individual glucose units. Thus, it is recognized that cyclodextrins are **unstable in acidic conditions** (see, highlighted sections of Appendix 2, Ullmann's Encyclopedia of Industrial Chemistry, Copyright © 2002 by Wiley-VCH Verlag GmbH & Co.). Weiner discloses a minoxidil composition having an acid component. It is my scientific opinion that the addition of an acid, as taught by Weiner to the composition of Navarro, would result in the degradation of the cyclodextrin ring and thus **destroy** the purpose of Navarro's invention.

11. For these reasons, I believe that the present invention is not rendered obvious by the disclosure of Navarro in view of Weiner, further in view of Leitch. The teaching of Leitch in no way supplements the deficiencies of Navarro in view of Weiner.

12. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true and further that these statement are made with the knowledge that willful false statements and the like so made may jeopardized the validity of the application or any patent issuing thereon.



Albert Zorko Abram

8th June, 2004

Date

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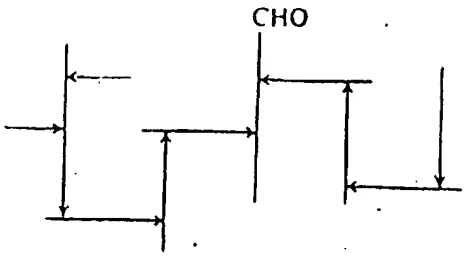

Amylopectin

Glycogen, the form in which carbohydrate is stored in animals to be released upon metabolic demand, has a structure very similar to that of amylopectin, except that the molecules appear to be more highly branched, and to have shorter chains (12–18 D-glucose units each).

Problem 39.16 Polysaccharides known as *dextrans* have been used as substitutes for blood plasma in transfusions; they are made by the action of certain bacteria on (+)-sucrose. Interpret the following properties of a dextran: Complete hydrolysis by acid yields only D-(+)-glucose. Partial hydrolysis yields only one disaccharide and only one trisaccharide, which contain only α-glycoside linkages. Upon methylation and hydrolysis, there is obtained chiefly 2,3,4-tri-*O*-methyl-D-glucose, together with smaller amounts of 2,4-di-*O*-methyl-D-glucose and 2,3,4,6-tetra-*O*-methyl-D-glucose.

Problem 39.17 Polysaccharides called *xylans* are found along with cellulose in wood and straw. Interpret the following properties of a sample of xylan: Its large negative rotation suggests β linkages. Complete hydrolysis by acids yields only D-(+)-xylose. Upon methylation and hydrolysis, there is obtained chiefly 2,3-di-*O*-methyl-D-xylose, together with smaller amounts of 2,3,4-tri-*O*-methyl-D-xylose and 2-*O*-methyl-D-xylose.

39.10 Cyclodextrins

When starch is treated with a particular enzyme (the amylase of *Bacillus macerans*), there is formed a mixture of *cyclodextrins*: polysaccharides of low molecular weight belonging to the general class called *oligosaccharides* (*oligo* = few).

A cyclodextrin consists of six, seven, eight, or more D-glucose units joined through 1,4-*alpha* linkages in such a way as to form a ring—a chain bracelet each link of which is a pyranose hexagon. These rings are doughnut-shaped, much as crown ethers are (Sec. 19.10), but with a number of important differences. The smallest of them, α-cyclodextrin, has a diameter about twice that of 18-crown-6, and its hole (4.5 Å across) is about twice as broad.

This hole is tapered slightly, so that the molecule is shaped like a tiny pail with the bottom knocked out (see Fig. 39.4, on the next page). Making up the sides is a loop of six or more hexagons, each one lying roughly in the plane of the sides; the depth of the pail is thus the width of the pyranose ring. Outside the pail, around the "upper", larger rim lie the secondary —OH groups of C-2 and C-3; around the "lower", smaller rim lie the primary —OH groups of C-6, that is, the $-CH_2OH$ groups. The inside of the pail consists of three bands, one on top of another: two bands of C—H's and, in between, a band of glycosidic O's.

Like a crown ether, a cyclodextrin can act as a host to guest molecules. Indeed, it was in connection with this property of cyclodextrins that the phenomenon now

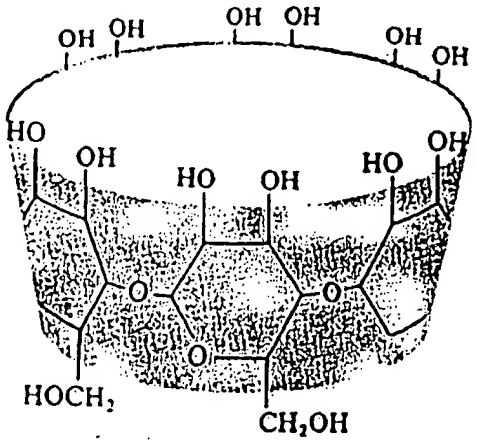

Figure 39.4 A schematic representation of α-cyclodextrin. The secondary —OH groups face outward about the "upper" rim; the —CH_2OH groups face outward about the "lower" rim. The cavity is lined with C—H's and glycosidic O's in three bands lying one above another.

known as the host–guest relationship was first recognized. But, in contrast to a crown ether, a cyclodextrin has a polar, hydrophilic outside and a relatively non-polar lipophilic inside. This leads naturally to two important results: (a) into its lipophilic interior a cyclodextrin typically takes as a guest, not an ion, but a non-polar organic molecule or the non-polar end of an organic molecule; and (b) its hydrophilic exterior confers water solubility on the resulting complex. How well a guest molecule is accommodated depends upon its size and polarity, and the size of the particular cyclodextrin.

Cyclodextrins can be used: to catalyze organic reactions, often with regioselectivity and a degree of stereoselectivity; and, most important, as comparatively simple models by which to study the action of enzymes.

The effects of cyclodextrins on chemical reactions can arise in a number of ways.

(a) They can simply hide certain parts of a guest molecule and expose other parts.

(b) They can change the conformation of the guest.

(c) Their lipophilic lining provides a non-polar medium for the guest—but within a polar solvent.

(d) Their —OH groups can participate in the reaction: either directly—as bases and nucleophiles or as hydrogen-bonding sites—or via transient intermediates (esters, for example) formed by reaction with the host or with the attacking reagent.

The particular usefulness of cyclodextrins as enzyme models comes from the fact that, like enzymes (see, for example, Sec. 41.2), they first *bind* the substrate and then, through substituent groups, *act upon it*: clearly, an example of symphoria.

Problem 39.18 The structure of cyclodextrins is shown, not only by x-ray analysis, but also by evidence of the kind we have already dealt with. Predict in detail the response expected from cyclodextrins to each of the following reagents or analyses: (a) Fehling's solution; (b) acidic hydrolysis; (c) methylation followed by acidic hydrolysis; (d) periodic acid; (e) molecular weight determination.

Cyclodextrins

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Ullmann's Encyclopedia of Industrial Chemistry

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3. Properties

Physical Properties. Selected physical properties of a-, b- and g-CD are listed in Table 1.

Table 1. Physical properties of the most important cyclodextrins

	a-Cyclodextrin [10016-20-3]	b-Cyclodextrin [7585-39-9]	g-Cyclodextrin [17465-86-0]
Formula	$C_{36}H_{60}O_{30}$	$C_{42}H_{70}O_{35}$	$C_{48}H_{80}O_{40}$
Molecular mass	972.85	1135.00	1297.14
Solubility in water (25 °C), g/100 mL	14.5	1.85	23.2
Crystal water, wt %	10.2	13.2 – 14.5	8.13 – 17.7
$[\alpha]_D^{25}$, °	+ 148	+ 162	+ 177
mp, °C	> 200 °C	> 200 °C	> 200 °C
pK_a value (25 °C)	12.331	12.202	12.081

Cyclodextrins are insoluble in alcohols, ketones, ethers, chlorinated hydrocarbons, and aliphatic and aromatic hydrocarbons.

Chemical Properties [3]. Cyclodextrins are chiral, nonreducing oligosaccharides. Upon oxidation with periodate the glucose rings are cleaved; neither formic acid nor formaldehyde is produced. The only degradation product of all cyclodextrins in acidic solution is glucose. The hydrolysis rate follows the order g > b > a. Under acidic conditions cyclodextrins are hydrolyzed more slowly than maltooligosaccharides. The glycosidic bond in cyclodextrins is hydrolyzed by a-amylase but not by b-amylase. The rate of enzymatic hydrolysis is fastest with g-CD, followed by b-CD and a-CD. All cyclodextrins are very stable and highly soluble in alkaline solution (pH > 14). In fact the solubility in water can be highly increased in basic solutions. Under nitrogen atmosphere cyclodextrins are stable up to 250 °C [4].

Substitution of hydrogen of the primary and secondary hydroxyl groups leads to cyclodextrin derivatives. Most reactions are carried out in aqueous solutions (all mentioned in Fig. 4 except acetylations). Other suitable solvents are dimethyl sulfoxide, dimethyl formamide, and pyridine.